REMARKS

This responds to the Final Office Action dated August 14, 2007.

Claims 1 and 11 are amended. Claims 1-3, 6, 11-13, and 16 are now pending in this application. With respect to the art rejections as set forth below, Applicant generally reiterates the remarks made in response to the previous Office Action.

§102 Rejection of the Claims

Claims 1-3, 6, 11-13 and 16 were rejected under 35 U.S.C. § 102(e) for anticipation by Casavant et al. (U.S. Publication No. 2004/0088015A1). The rejections are traversed and reconsideration is respectfully requested.

The Final Office Action, in response to Applicant's arguments put forth in response to the previous Office Action states that:

> At paragraph 73, Casavant discloses that control signals are utilized to ensure that the phrenic nerve is capture and the diaphragm is contracted. Based on this disclosure, it is inherent that respiratory activity is detected, otherwise the control signals would be unnecessary.

The type of respiratory activity that is being "detected" by ensuring that diaphragmatic pacing is achieving capture, however, is not *spontaneous* respiratory activity as recited by the claims. Applicant respectfully asserts that the claims are not anticipated due to lack of this element.

The Final Office Action also states that "(f)urther, regarding Applicant's assertion that detection of the pressure and oxygen saturation of the blood is not indicative of respiratory activity, the Examiner takes the position that the system of Casavant is capable of detecting respiratory arrest based on the pressure and oxygen saturation of the blood because a decrease in these values indicate that a patient is not obtaining the necessary oxygen, and thereby not breathing effectively." What is actually Applicant's position, however, is that detection of the oxygen saturation or pressure of the blood *during ventricular fibrillation* is not indicative of respiratory activity. As stated previously, while blood oxygen concentration may be reflective of respiratory activity under normal physiological circumstances, this is not the case when ventricular fibrillation is present. When ventricular fibrillation is present, the pumping action of

the heart is so severely compromised that little or no blood flows through the pulmonary and systemic circulations, and respiratory activity thus has no effect upon blood oxygen concentration. In support of this assertion, Applicant submits herewith as Exhibit A, an article from the British Journal of Anaesthesia entitled "Cerebral oxygenation measured by near-infrared spectroscopy during circulatory arrest and cardiopulmonary resuscitation." Fig. 1 of that article and the accompanying description clearly demonstrates that blood oxygen saturation falls when ventricular fibrillation occurs even while the patent is being artificially ventilated by CPR. Claims 1-3, 6, 11-13 and 16 all recite that spontaneous respiratory activity is monitored during ventricular fibrillation while the output capacitor is charging, and those claims are therefore not anticipated by Casavant.

§103 Rejection of the Claims

Claims 1-3, 6, 11-13 and 16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Scheiner (U.S. Patent No. 6,415,183) in view of Min et al. (U.S. Patent No. 5,836,976). The rejections are traversed and reconsideration is respectfully requested.

The Final Office Action, in response to Applicant's arguments put forth in response to the previous Office Action states that:

> Regarding the rejection of the claims under 35 USC 103(a) as being unpatentable over Scheiner in view of Min, Applicant argues that Min fails to disclose delivering diaphragmatic pacing during the ventricular refractory period after a ventricular sense if respiratory arrest is detected subsequent to the termination of the ventricular fibrillation by the shock pulse. The Examiner respectfully disagrees as Min discloses that the therapy is timed with respect to the cardiac cycle in order to avoid delivery of therapy during a vulnerable period of the cardiac cycle (see col. 6, ln. 18-22). Therefore, Min in fact discloses delivering diaphragmatic pacing during the ventricular refractory period if respiratory arrest is detected subsequent to the termination of the ventricular fibrillation.

Applicant believes that the above-quoted statements mischaracterize the teachings of Min. The Min reference does not discuss anything relating to the delivery of diaphragmatic

pacing during the ventricular refractory period after a ventricular sense if respiratory arrest is detected subsequent to termination of the ventricular fibrillation by the shock pulse as recited by claims 1-3, 6, 11-13 and 16 for at least the following reasons. First, the Min reference does not discuss delivering diaphragmatic pacing in conjunction with delivering shock pulses for terminating ventricular fibrillation as recited by the pending claims. Instead, the reference deals primarily with the delivery of cardioversion shocks (i.e., shocks delivered in synchrony with the cardiac cycle) for terminating atrial fibrillation and ventricular tachycardias, not ventricular fibrillation, and confines the discussion of diaphragmatic pacing to that context. Second, the reference contains no discussion relating to the delivery of diaphragmatic pacing for any reason but to synchronize the delivery of cardioversion shocks with the respiratory cycle. It therefore contains no discussion relating to the delivery of diaphragmatic pacing after termination of an arrhythmia of any kind, much less ventricular fibrillation.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (847) 432-7302 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date October 29, 2007

By /J Kevin Parker/
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop RCE, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 29 day of October 2007.

Kate Gannon

Name

Signature

EXHIBIT A

British Journal of Anaesthesia **91** (3): 438–42 (2003)
DOI: 10.1093/bja/aeg181

Cerebral oxygenation measured by near-infrared spectroscopy during circulatory arrest and cardiopulmonary resuscitation

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We measured cerebral oxygenation by near-infrared spectroscopy (NIRS) during an unexpected cardiac arrest and successful cardiopulmonary resuscitation (CPR). A 4-yr-old girl with cyanotic congenital heart disease developed an arrhythmia during cardiac catheterization with subsequent circulatory arrest. Continuous monitoring of cerebral oxygenation showed marked changes in oxygen status immediately after the beginning of the tachyarrhythmia. After 1 min of circulatory arrest, a decrease in oxygenated haemoglobin concentration and cytochrome oxidase signal indicated a critical reduction of oxygen tension. With the beginning of CPR, a rapid increase in cytochrome oxidase oxygenation was observed. Previous values, however, were only restored when sinus rhythm was obtained after successful cardiac defibrillation. Our observations suggest that non-invasive cerebral NIRS measurement gives useful additional real-time information on cerebral oxygenation during cardiac arrest and CPR.

Br J Anaesth 2003; **91**: 438–42

Keywords: brain, cerebral oxygenation; children; complications, circulatory arrest; heart, resuscitation; measurement techniques, near-infrared spectroscopy

Accepted for publication: April 12, 2003

Near-infrared spectroscopy (NIRS) is a non-invasive method to measure oxygenation in a localized tissue field and measures the transmission of infrared light through biological tissue. This indicates changes in oxygenation and the concentration of tissue chromophores such as total haemoglobin concentration (tHb) with its constituent oxygenated haemoglobin (HbO_2) and deoxygenated haemoglobin (HHb) and cytochrome oxidase (CytOx), which is the terminal enzyme in the mitochondrial respiratory chain. Changes in chromophore concentrations are quantified by using the modified Lambert–Beer law.[1] NIRS is becoming used in paediatric intensive care medicine to obtain real-time information on tissue oxygenation, particularly in preterm and term neonates to investigate brain, liver and splanchnic tissue oxygenation.[2–4]

The NIRO 300 (Hamamatsu Phototonics, Japan), which uses spatially resolved spectroscopy (SRS) as an algorithm,[5 6] measures a tissue oxygenation index (TOI) and a tissue haemoglobin index (THI) as absolute values without the need to know a path-length factor. TOI reflects the ratio of $k \times HbO_2/(k \times HbO_2 + k \times HHb)$ and THI reflects the denominator $k \times HbO_2 + k \times HHb$, where k is an unknown but constant tissue parameter.[5] TOI represents the tissue saturation and is measured in percent, whereas THI is an absolute figure of the total haemoglobin but, due to the factor k, measured in arbitrary units. As it is an absolute value, its changes from one measuring point to another can be measured as a percentage. We describe our observations on cerebral NIRS monitoring in a patient who needed CPR during cardiac catheterization.

Case report

A 4-yr-old girl (18 kg) with an Ebstein malformation was to have diagnostic cardiac catheterization. The child suffered from increasing exertional dyspnoea and cyanosis with a transcutaneous peripheral oxygen saturation of <90%. An episode of supraventricular tachycardia was suggestive of a pre-excitation syndrome. The initial aim of NIRS recording was to investigate the effect of deep conscious sedation on cerebral oxygenation. The study was approved by the Ethics Committee of the Medical Faculty, and written informed consent was given by the parents.

The NIRS probe was placed on the forehead in the supraorbital region receiving reflected light from the frontal neocortex. The patient was given midazolam and ketamine i.v. Monitoring was by ECG and pulse oximetry. Blood pressure was measured non-invasively at intervals of 5 min. During the examination a catheter was introduced into the right atrium and through the atrial septal defect into the left atrium. This triggered a supraventricular tachycardia (heart rate=230 beats min^{-1}). A sudden decrease in HbO_2, tHb, CytOx, TOI and THI was observed. Figure 1 shows how the NIRS values changed.

The NIRS output showed desaturation of the TOI from 65% to 13%, and the THI decreased from 82 to 55 arbitrary units, indicating a decrease of 33% in the total haemoglobin content in the measured area. HbO_2 decreased by 37 $\mu mol\ litre^{-1}$ and the HHb signal increased by 24 $\mu mol\ litre^{-1}$. CytOx signal showed a rapid decrease of 1 $\mu mol\ litre^{-1}$ from baseline (Fig. 1, event 2). Mean arterial pressure decrease to <20 mm Hg and peripheral pulse oximetry did not show any valid signals because of the low pulse pressure. After two unsuccessful attempts at cardioversion, ventilation and cardiac compressions were started and with an increase in HbO_2, tHb, THI and CytOx, TOI values started to increase with a short latency (Fig. 1, event 3). During this time ventricular fibrillation started (Fig. 1, event 4). After 24 min of CPR, the ventricular fibrillation was stopped by defibrillation and followed by a supraventricular tachycardia (heart rate=190 beats min^{-1}) with a mean arterial pressure of 60 mm Hg. Values for HbO_2, tHb and TOI started to decline again with the beginning of tachycardia, while HHb values increased once again (Figure, event 5). The CytOx signal demonstrated slight fluctuations at a greater value compared with the baseline values before the resuscitation (Δ0.8 $\mu mol\ litre^{-1}$). Cardioversion led to sinus rhythm and blood pressure increased to 90 mm Hg. A slight increase in HbO_2 and TOI and a decline in HHb were seen (Fig. 1, event 6). CytOx signal started to decline, but NIRS monitoring was interrupted because the patient was transferred to the intensive care unit. Under therapy with propafenon no further cardiac tachyarrhythmia occurred. Corrective surgery of the congenital heart defect was carried out and the child was discharged from intensive care with no neurological deficits.

Discussion

In our patient, a decrease of the NIRS values (HbO_2, CxtOx, THI, TOI) was noted before the circulatory situation became apparently severe. The pulse oximeter failed to provide data on arterial saturation during the resuscitation as would be expected because of the poor signal whereas the NIRS signal changes were immediately visible. Changes in CytOx redox state are only seen when the availability of oxygen at the cellular intramitochondrial level has decreased to critical values.[7 8] A decrease of CytOx correlated with a decreased brain energy state and may indicate impending cellular injury.[9] The immediate decrease of intravascular cerebral oxygen differs clearly from the slow changes following circulatory arrest in deep hypothermia during corrective cardiac surgery.[2]

The reason for an increase in CytOx to values greater than baseline after restoration of spontaneous circulation remains unclear. A possible explanation could be the compensatory reoxygenation following an ischaemic period or the influence of mechanical ventilation with oxygen 100%.

NIRS has been studied in cardiac arrest in 18 patients arriving in an emergency department with circulatory arrest or shortly after restoration of spontaneous circulation.[10] The

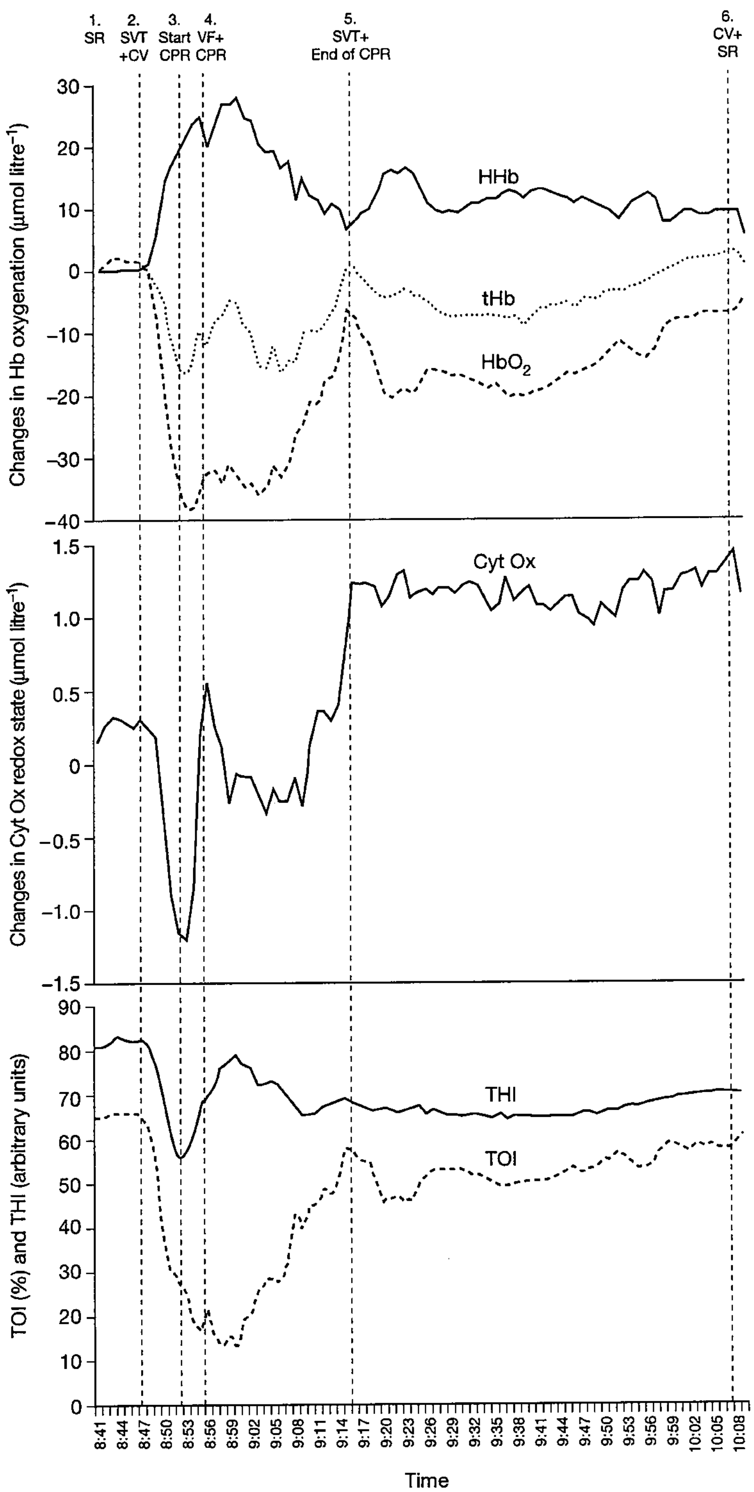

Fig 1 Measurements of cerebral oxygenation data. Oxygenated (HbO_2), deoxygenated (HHb) and total haemoglobin (tHb), cytochrome oxidase (CytOx) and tissue oxygenation index (TOI). Display of the full measurement (numbered dotted lines show the different events): 1=baseline with sinus rhythm (SR); 2=beginning of supraventricular tachycardia (SVT) and cardioversion (CV); 3=beginning of cardiopulmonary resuscitation (CPR); 4=ventricular fibrillation (VF) and CPR; 5=defibrillation (SVT, end of CPR); 6=cardioversion (SVT was cardioverted into SR). When low cardiac output occurred (event 2) an immediate change of intravascular oxygen was shown by a decrease in tHb, HbO_2, CytOx, TOI and THI. A decrease in CytOx indicated reduced oxygen in the cell, which was reversed by CPR (event 3). All values started to normalize when spontaneous circulation was restored.

authors reported that if regional cerebral oxygen saturation (Sr_{O_2}) is small after cardiac arrest, there is a greater mortality. Recently published data[11] describe cerebral oximetry in a patient with cerebral infarction and circulatory arrest, with a difference between the NIRS signals obtained from the centre of the stroke compared with the non-stroke areas. The saturation in an ischaemic area that is metabolically inactive can be normal because oxygen extraction does not occur from cerebral venous blood, which can also be from other adjacent brain regions that are perfused. Thus, the interpretation of NIRS data may be difficult in patients with cerebral stroke without the use of other imaging methods.[11] Our data support observations of another report where Sr_{O_2} decreased from 60% to 41% in a patient with circulatory arrest.[12] Systemic perfusion was restored with cardiopulmonary bypass and the changes during hypoxaemia were reversed. The authors inferred that NIRS might be useful to determine the effectiveness of CPR. None of the reports[10–12] that measured cerebral oxygenation during cardiac arrest commented on CytOx changes because they used a different transcranial NIRS monitoring system (INVOS 3100, Somanetics Inc., Troy, MI, USA). A recent study compared two different near-infrared spectrophotometers (INVOS 4100 and the NIRO 300) measuring cerebral oxygen saturation during changes of cerebral blood flow induced by carbon dioxide challenge.[13] The INVOS 4100 and the NIRO 300 showed a significant linear correlation for values of Sr_{O_2} and TOI during carbon dioxide alteration, but Bland–Altman analysis[14] showed that the individual values and the relative changes displayed by the two devices were not equivalent.

Discrepancies between persisting bowel desaturation measured with NIRS and short episodes of systemic desaturation were reported in neonates.[15] We could not measure the circulation and systemic saturation continuously to detect differences between cerebral and systemic saturations.

Studies of the relationship between cerebral measurements with other devices and regional cerebral oxygenation measured by spatially resolved NIRS give different results.[16 17] Measurements of jugular bulb oxygen saturation (Sj_{O_2}) measured by co-oximetry and TOI measured by NIRO 300, do not agree well despite a statistically significant correlation.[16] The NIRS cerebral monitoring measures TOI in a small region of the *cerebral* microvasculature, whereas Sj_{O_2} reflects a more global measurement, so inhomogeneous distribution of blood or metabolic activity will reduce the agreement between the two methods.[18] In addition, the TOI signal reflects an average of arterial (25%), capillary (5%) and venous (70%) blood. Cerebral cortex haemoglobin saturation, measured directly by the spatially resolved method, reflects predominantly the saturation of the intracranial venous compartment of circulation.[17] Unfortunately, we did not have other measurements of brain oxygenation in our patient to verify that the decrease in TOI represented a change in cerebral oxygen saturation. Sj_{O_2} and TOI may measure different entities, so that although there is a significant correlation between Sj_{O_2} and TOI, the two measures are not interchangeable.[16]

Our observations show that non-invasive cerebral NIRS measurement gives useful real-time information on cerebral oxygenation during cardiac arrest and CPR and this deserves further investigation.

Acknowledgement

We thank Anne M. Gale of the Deutsches Herzzentrum Berlin for editorial assistance.

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